REMARKS

Prior to this amendment claims 2-10 and 27-31 were pending. Claims 27, 28, 29 and 30 are amended for clarity. Claims 33-37 are new. Support for the claim amendments and new claims is found in claims 1, 11 and 15 as filed, at p. 21, lines 9-12, p. 23, lines 10-19. Applicants submit that no new matter is introduced by way of these amendments.

Response to Detailed Action

Claim Interpretation

The Examiner indicated that "[t]he term 'first and second linkers' is interpreted as linkers which may be the same, as there is no requirement that they have to be different." Applicants agree with this interpretation.

The Examiner indicated that "[t]he term 'chip' in claim 29 is interpreted as any substrate" as "it is used interchangeably with 'substrate' in the claim." Applicants submit that the issue is moot following amendment of the claim.

Rejections under 35 U.S.C. § 102

Claims 27, 30, 31, 3-6 and 9 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Beattie (U.S. Patent No. 6,156,502). Applicants respectfully traverse.

Beattie is drawn to a method of "arbitrary sequence oligonucleotide fingerprinting (ASOF)". This, in essence, relies on the use of random sequences to create a hybridization "fingerprint" that can be compared between two samples for differences. This eliminates gel electrophoresis as a step in polymorphic marker analysis.

In contrast, the present invention is directed to making pools of oligonucleotides by cleaving them off of a substrate (or substrates) into at least one pool, and then using the pool for detecting target sequences.

Specifically, claim 27 is drawn to a method for multiplex detection of target nucleic acids comprising providing a substrate comprising at least first and second different oligonucleotides linked to the substrate through first and second cleavable linkers, respectively, cleaving the first

and second linkers, thereby releasing the first and second oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising the first and second different oligonucleotides, contacting the first and second different oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby the first and second target nucleic acid hybridize with the first and second oligonucleotides, whereby the target nucleic acids are detected.

Also, claim 30 is drawn to method for multiplex detection of target nucleic acids comprising cleaving at least first and second different oligonucleotides linked to a substrate through at least a first cleavable linker from the substrate, thereby releasing the first and second oligonucleotides from the substrate generating a pool of oligonucleotides comprising the first and second different oligonucleotides, contacting the first and second oligonucleotides with a composition that includes the first and second target nucleic acid, whereby the first and second target nucleic acids hybridize with the first and second oligonucleotides, whereby the target nucleic acids are detected.

As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference."

Here, Applicants respectfully submit that each element of the claimed invention is not present in Beattie.

Specifically, the Examiner asserts that Beattie teaches providing a substrate and at least first and second different oligonucleotides linked to said substrate through first and second cleavable linkers, respectively, because Beattie teaches providing a controlled pore glass support with a set of oligonucleotide probes linked to the substrate via the 3'-amino linker. The Examiner cites to Col. 8, lines 30-36, Col. 12, lines 60-62, and Col. 16, lines 39-42.

However, the cited sections of Beattie refer to the way an array is constructed for use in the Beattie "arbitrary sequence oligonucleotide fingerprinting" (ASOF) technique. As was well known in the art, and described by Beattie, controlled pore glass (CPG) was (and is) used to synthesize individual oligonucleotides. Beattie teaches the use of CPG to synthesize an oligonucleotide with a 3'-amino group. Each oligonucleotide is then cleaved off the CPG and spotted onto the surface (using the amino group), to make an array, as described in Column 12,

line 65 to Column 13, line 8. The passage was only partially cited by the Examiner; the full citation includes the cleaving of a 3'-amine labeled oligonucleotide from the CPG, cleaning the surface for attachment, and then "applying a small droplet of each oligo solution onto the clean, dry glass surface . . ." (emphasis added; see Column 13, lines 3-4). Similarly, Column 13, lines 17-32 goes on to discuss methods of generating the array, using manual spotting or robotic equipment. These cited passages make it clear that each "cleaved" oligonucleotide is spotted individually.

Furthermore, if the synthetic reactions were "mixed" or "pooled", the result would be that there would be a mixture of different oligonucleotide sequences at any particular spot on the array. Beattie clearly teaches that this is not the case.

> A key feature, common to *all* embodiments of the arbitrary sequence oligonucleotide fingerprinting technique of the present invention, is the use of a set of arbitrary sequence oligonucleotide probes, *each* sequence located at a *specific site* on a hybridization support via binding of the short strands to the surface at one end.

(Column 4, lines 5-10, emphasis added). In teaching that all embodiments of the ASOF technique require that each sequence is located at a specific site, Beattie clearly demonstrates that any pools of oligonucleotides do not include first and second different nucleotides. Accordingly, Beattie fails to teach a method that includes generation of a pool of oligonucleotides comprising said first and second different oligonucleotides as claimed.

The Examiner also alleges that there is a description of removing different oligonucleotides from a support via cleavable linkers. However, the Examiner has pointed to no evidence that the methods disclosed in Beattie are used for "generating a pool of oligonucleotides comprising said first and second different oligonucleotides" as claimed. Rather, the discussion in Beattie of cleaving oligonucleotides occurs in the context of preparing oligonucleotides for attachment to arrays, in which case the oligonucleotides would have been kept separate from each other so that each location of the array had a single discrete oligonucleotide sequence. Accordingly, Applicants submit that Beattie fails to teach each and every limitation of claims 27 and 30. Applicants respectfully request that the Examiner withdraw the rejection.

Rejections under 35 U.S.C. § 103

Claims 2-10 and 27-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Holmes (U.S. Patent No. 5,679,773; cited in the Office Action of August 13, 2003) and Beattie (U.S. Patent No. 6,156,502).

Beattie is described above.

Holmes is directed to methods for solid phase synthesis of organic molecules. Holmes discloses reagents having attached linking groups, including cleavable linkers, which are useful in solid phase syntheses of high density arrays of organic molecules.

In contrast, as outlined above, the present invention is directed to making pools of oligonucleotides by cleaving them off of a substrate (or substrates) into at least one pool, and then using the pool for detecting target sequences.

The Examiner's position appears to be that Holmes teaches each element of these claims except contacting oligonucleotides with target nucleic acids. However, the Examiner suggests that Beattie teaches contacting oligonucleotides with target nucleic acids and that the combination of these two references renders the claims obvious. Applicants respectfully traverse.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Initially, Applicants note that in contrast to the Examiner's characterization of the references, the combination of Beattie and Holmes does not teach or suggest all of the elements of the claims. That is, as noted above with respect to Beattie, there is no teaching in Holmes, Beattie or the combination of the two of a method that includes cleaving linkers to arrive at a "pool of oligonucleotides comprising said first and second different oligonucleotide" as claimed.

The Examiner points to sections of Holmes that describe cleaving linkers to release oligonucleotides. However, there is no teaching or suggestion in Holmes, taken alone or in combination with Beattie, of generating a pool of oligonucleotides comprising first and second different oligonucleotides as claimed. In this regard, the mere assertion at column 6, lines 36-37 that compounds synthesized on beads provided on a surface may be released upon completion of a synthesis does not teach or suggest generating a pool of different oligonucleotides because the compounds would have likely been released individually. This would especially follow from the passage at column 12, lines 6-16 cited by the Office which describes photocleavage of linking groups for characterization purposes following bioassay because Holmes does not describe methods for characterizing mixtures of probes following release from their arrays.

Moreover, as described above in response to the anticipation rejection, Beattie fails to cure the deficiency of Holmes because there is no disclosure in Beattie of generating a pool of oligonucleotides comprising first and second different oligonucleotides. Accordingly, Applicants submit that each element of the claims is not present in the cited references and a *prima facie* case of obviousness has not been established.

Moreover, even assuming, *arguendo*, that all of the claim elements were present, Applicants submit that the requisite motivation to combine references is absent. The Examiner appears to rely on the teaching of Beattie that the ASOF assay was used in polymorphic marker analysis, species identification and transcriptional profiling without the need for electrophoresis and that therefore, one of ordinary skill in the art would be motivated to combine the assay of Beattie with the oligonucleotides cleaved from solid support of Holmes, assuming *arguendo*, that Holmes disclosed such oligonucleotides cleaved from a solid support which Applicants maintain it does not (see above). However, as set forth above in response to the anticipation rejection, in teaching that *all* embodiments of the ASOF technique require that each sequence is located at a specific site (see column 4, lines 5-10), Beattie clearly teaches away from the generation of a pool of oligonucleotides comprising said first and second different oligonucleotides as claimed.

To this end, Applicants respectfully remind the Examiner that "[i]t is improper to combine reference when the references teach away from their combination." In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). As noted previously, Beattie clearly teaches away from the generation of a pool of oligonucleotides. Thus, to the extent that Holmes

allegedly discloses cleavage of oligonucleotides from a support, Applicants submit that it is improper to combine these references to reach the claimed invention.

Accordingly, Applicants submit that there is insufficient motivation in the prior art to combine the references to reach the claimed invention. Moreover, Applicants submit that the references alone or in combination fail to teach or suggest each element of the claims. As such, a *prima facie* case of obviousness has not been established. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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